REMARKS

Status of the Claims

Claims 4-10 were previously withdrawn. Applicants respectfully reserve the right to pursue the non-elected subject matter in one or more continuation, continuation-in-part, and/or divisional applications pursuant to 35 U.S.C. §§ 120 and 121. Claims 1-3 are currently pending.

Claim Rejection— 35 U.S.C. § 103

Claims 1-3 were rejected under 35 U.S.C. § 103(a) as unpatentable over Chen *et al.* (WO 96/39176) in view of Katz (US Patent No. 4,950,469). Applicants respectfully disagree and traverse this rejection. The Office Action states that

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Chen et al. teach that oral tolerance to autoantigens can be used to treat antibody mediated autoimmune disease wherein the disease involves antibodies which bind the pertinent autoantigen whilst Katz teaches that [] rheumatic fever involves an autoimmune antibody response caused by anti streptococcal antibodies which cross react with human tissues wherein the streptococcal antigens would function as an autoantigen.

(Office Action, p. 2-3.)

A proper obviousness rejection of patent application claims under 35 U.S.C. § 103(a) requires a showing by the USPTO that the invention defined in the rejected claim(s) as a whole is obvious in view of one reference or a combination of the references. M.P.E.P. § 2142. Three basic criteria must be met to support a *prima facie* case of obviousness: (a) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference(s) teachings; (b) there must be a reasonable expectation of success; and (c) the prior art reference (or references when combined) must teach or suggest all the claim features. M.P.E.P. § 2143. Here, the references cited in the Office Action do not individually or in combination suggest to a person of ordinary skill in the art the invention of the Applicants' claims 1-3.

Applicants respectfully assert that Chen *et al.* and the Katz, whether alone or in combination, do not teach or suggest all of the features present in Applicants' claimed invention.

Neither Chen *et al.* nor Katz teaches "A process for producing selective immune down regulation in a subject to *an infectious bacterial agent* comprising introducing to said subject a reagent or a combination of reagents capable of producing selective immune down regulation and comprising a component or components or fragments thereof of said infectious agent." Chen *et al.* teach a method for suppression of specific Th2 and Th1 immune responses and antibody production, as they apply to antibody-mediated immune diseases, via the oral route. Chen *et al.*, page 1, lines 15-18; page 4 lines 31-33. Chen *et al.* does not teach the immune down regulation to an infectious agent comprising introducing to the subject a component or fragment of the infectious agent. In fact, no infectious agents are listed in the table of Antigens that May Be Used to Induce Tolerance, found on pages 17-18.

Applicants previously argued that Chen *et al.* does not teach the present invention because the reference relates to high-dose feeding while the inventors of the instant application have shown that high does feeding is ineffective. Unlike high-dose feeding, low-dose feeding inhibited both the humoral and cellular immune responses. *See* Specification, Example 1, p. 39, paragraph 1. The Examiner countered by stating that Chen *et al.* is not limited to high dose feeding. Office Action, page 3. Applicants respectfully disagree. Chen *et al.* contemplates a method for treating a mammal suffering from an antibody-mediated autoimmune disease comprising orally administering to the mammal at least one autoantigen and continuing the administration for a period of time until the Th2 cell mediated autoimmune response is suppressed. *See* Chen *et al.*, page 5, lines 12; page 5, line 33-38; page 12, lines 5-9. The authors continue by stating that suppression of the Th2 response is only accomplished through the delivery of a relatively high amount of antigen. *See* Chen *et al.*, page 14, lines 35-38; page 15, line 7 through page 17, line 2. The Examiner continues in stating that Applicants' Example 1 is drawn to a specific dosage range which is not the dosage encompassed by the term "large amounts of antigen" as per Chen *et al.* Office Action, page 3-4. Applicants' Example 1 contemplates a "higher antigen dose" of 50-100 mg daily. *See* Specification, Example 1, page 38, final paragraph, "Effect of Antigen Dose". This is in fact a lower dose than those utilized in the Chen *et al.* Examples 1-5 (mice were exposed to unlimited amounts of sterile drinking water

containing 1 mg/ml antigen, consuming at least four doses of 0.25 ml per day). *See* Chen *et al.*, page 22, lines 4-11. In addition, Chen *et al.* Examples 6-10 and Examples A, B and C utilized concentrations up to 500 mg per dose. Thus, the "high dose" concentrations found by Applicants to be less effective are in fact lower than those contemplated in Chen *et al.* The Examiner then concludes that Example 1 is irrelevant to the invention under consideration because it is not drawn to the claimed method using a bacterial antigen. Office Action, page 3. Although Example 1 is not drawn directly to the claimed invention of the use of bacterial antigens, it is one illustration of how Chen *et al.* (also not drawn to the use of bacterial antigens) differs from Applicants' present invention.

In addition, Chen *et al.* only describes the use of artificial antigens. The Examiner has cited a passage from Chen *et al.* that expands the definition of autoantigen to include "antigenic substances that induce conditions having the characteristics of an autoimmune disease *when administered* to mammals" (emphasis added). Office Action, page 3. The Examiner takes the position that this would describe the streptococcus antigens. However, the context of this sentence should be appreciated. Although Chen *et al.* may describe the use of oral tolerization for disease, the patent is also describing the use of animal models of autoimmunity that are artificially induced systems. Chen *et al.* state "The T-cells of the subject react to an antigen they recognize regardless of whether the antigen is endogenous (as in autoimmunity) or not (as in the present experimental models)." *See* Chen *et al.*, pg 13, lines 7-10. Thus, Chen *et al.* describes antigens that do not cause an autoimmune disease per se, but can induce a condition that mimics an autoimmune disease after administration to a test animal. There is no description of using an antigen that causes induction of a true autoimmunity disease by means of a natural infective route (such as by a Strep infection) as opposed to an "administered" antigen in experimental models where the antigen serves as not only as the oral tolerance inducer but the "target" for reactivity by acting as an immune surrogate for an autoantigen. OVA was used as the tolerizing agent in a system where there was no OVA-like autoantigens. In addition, Chen *et al.* requires that OVA be administered as the target. Chen *et al.* utilized an artificial system where transgenic mice were developed that expressed a T-cell receptor specific to OVA (Va13/Vb8.2TcR). *See* Chen *et al.*, Example beginning on page 14. Additionally, each of Examples A through D used

autoantigen preparations that were essentially derived from mammalian proteins. *See* Chen *et al.*, Examples A through D, beginning on page 40.

Applicants submit that the references cited in the Office Action do not individually or in combination suggest to a person of ordinary skill in the art the invention of the Applicants' claims 1-3. The Office Action fails to establish why or how it would have been obvious to one of ordinary skill in the art at the time of the invention to combine Chen *et al.* with Katz resulting in a process for producing selective immune down regulation in a subject to an infectious bacterial agent comprising introducing to said subject a reagent or a combination of reagents capable of producing selective immune down regulation and comprising a component or components or fragments thereof of said infectious agent, meeting all the limitations of claims 1-3.

Even if, *arguendo*, it were proper to combine the references (as Applicants vigerously dispute), it has not been established in the Office Action that the combination would have yielded a process that meets each and every limitation of the claims. The Katz reference does not cure the deficiencies of Chen *et al.* The Examiner cites Katz as teaching the use of strep A proteins as a source of autoantigens, "wherein the streptococcal antigens would function as autoantigens" Office Action, page 3-4. The Examiner then states "Thus the streptococcal antigen as per discussed by Katz *et al.*, would constitute an autoantigen as per the definition of said term in Chen *et al.*" Office Action, page 3-4.

Applicants respectfully disagree with the Examiner's characterization of Katz. Immediately preceding the discussion of rheumatic fever, Katz discusses the case of myasthemia gravis, describing that the particular autoantigen involved in this autoimmune disease is the acetylcholine receptor. Katz further states that this protein has been cloned and could be used in their invention. *See* Katz, col. 5, line 56 through col. 6, line 14. No mention is made of the identity and potential use of proteins from a causative agent. In fact, the target itself is used as the autoantigen. A similar situation exists with the discussion by Katz regarding the use of autoantigens involved in rheumatic fever. "Rheumatic fever is also believed to involve an autoimmune response to *streptococcal antigens that are expressed by other tissues* especially cardiac tissue." *See* Katz, col. 6, lines 14-16. As such, when Katz later describes "conjugates of antigens which specifically bind anti-strep A antibodies" (*See* Katz, col. 6, lines 18-20), the term

"antigens" refers to the target proteins in the subject. It is obvious that a streptococcal antigen that is defined solely by its ability to bind to an anti-strep Ab in and of itself is not likely to be useful since the vast majority of streptococcal proteins will have absolutely no antigenic correspondence with mammalian proteins. As such, the term "antigen" as used by Katz, refers to the aforementioned "antigens that are expressed by other tissues", *i.e.* autoantigens that resulted from a strep infections that "specifically bind to anti-strep-A antibodies". In a later sentence Katz states "As specific autoantigens are identified and isolated, D-GL conjugates thereof may also...."; and in the next sentence: "Such D-GL conjugates may include..... and the antigen.....". *See* Katz, col. 6, lines 24-32. It is clear that the reference to "antigen" refers to the autoantigen in the previous sentence. Nowhere does Katz describe the isolation and characterization of antigens derived from streptococcus itself that could be used with his system.

Additionally, Katz states that its disclosure relates to "receptor blocking technology" and a "cell-surface receptor binding molecule—D-GL conjugate of the cell surface receptor binding molecule and introducing such D-GL conjugates into the patient." *See* Katz, Abstract and col. 2, lines 59-62. In its brief discussion of rheumatic fever, Katz merely mentions the antigens of cardiac tissue to which "anti-Strep A antibodies" can bind. *See* Katz, col. 6, line 16. Katz states that "D-GL conjugates of antigens which specifically bind anti-Strep A antibodies, if injected . . . may be expected to interfere with the autoimmune response which is believed to be implicated in rheumatic fever . . . As specific autoantigens are identified and isolated, D-GL conjugates thereof may also interfere with the inflammation response and halt or diminish the rate of progress of the disease." *See* Katz, col. 6, lines 18-26. Autoantigens are "antigens that are expressed by [the patients'] tissue." *See* Katz, col. 6, lines 15-16. Nowhere does Katz teach or suggest the process of introducing into a subject a substance comprising components or fragments of an infectious *bacterial agent* for producing selective immune down regulation, as described in Applicants presently claimed invention.

Absent an explicit teaching or a suggestion in Chen *et al.*, it would not have been obvious to a person of ordinary skill in the art to modify the process described therein. Thus, a person of ordinary skill in the art would not have found it obvious to combine the teachings of the cited references because neither Chen *et al.* nor Katz teaches each and every limitation of the claims. Katz teaches only the use of an autoantigen and Chen *et al.* only the use of an artificial

autoantigen. Neither reference describes induction of oral tolerization by the use of a bacterial antigen that induces an autoimmune response. The improper combination of the references fail to suggest to a person of ordinary skill in the art the use of the process of Chen *et al.* to result in the process for producing selective immune down regulation of an infectious agent comprising introducing to said subject a reagent or a combination of reagents comprising a component or components or fragments the infectious agent, meeting all the limitations of claims 1-3.

To establish a *prima facie* case of obviousness of a clamed invention, the Office Action must establish that each limitation of the rejected independent and dependent claims is taught or suggested by the prior art. M.P.E.P. § 2143.03. The Office Action failed to do so at least because no evidence was presented that prior art teaches or suggests all limitations of the rejected claims. The brief discussion of strep-A antibodies would not provide the motivation to combine the cited references. A person of ordinary skill in the art would have no expectation of success in combining Chen *et al.* and Katz because the combination would not result in Applicants' presently claimed process for producing selective immune down regulation in a subject to an infectious bacterial agent comprising introducing to said subject a reagent or a combination of reagents capable of producing selective immune down regulation and comprising a component or components or fragments thereof of said infectious agent.

Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants respectfully submits that claims are in condition for allowance, and such disposition is earnestly solicited. Should the Examiner believe that any patentability issues remain after consideration of this Response, the Examiner is invited to contact the Applicants' undersigned representative to discuss and resolve such issues.

In the event that a variance exists between the amount tendered and that deemed necessary by the U.S. Patent and Trademark Office to enter and consider this Response or to maintain the present application pending, please credit or charge such variance to the undersigned's **Deposit Account No. 50-0206**.

Respectfully submitted,

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